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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1653	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/455,978	Applicant(s) ALAM ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-65* is/are pending in the application.

4a) Of the above claim(s) *7,8,17-47 and 55-63* is/are withdrawn from consideration.

5)☒ Claim(s) *48* is/are allowed.

6)☒ Claim(s) *1-6,11-15,50,53,64 and 65* is/are rejected.

7)☒ Claim(s) *12-16,49-54,64 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *06 December 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

As stated in Paper No. 18, in accordance with 37 CFR 1.126, the original second appearing claim 7 and 8 were renumbered as Claims 9 and 10 and the claims that followed were renumbered accordingly as shown in the attached copy of the claims as renumbered. Therefore, in the Preliminary Amendment filed June 25, 2001, Claims 9 and 10 (originally the second appearing claim 7 and 8) were cancelled, and renumbered Claims 64 and 65 (submitted as Claims 62 and 63) were added. Therefore, currently, Claims 1-8 and 11-65 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-6, 11-16, and 48-54 in Paper No. 22 is acknowledged. The traversal is on the ground(s) that the claims are closely related and require common areas of search and consideration therefore there is no serious search burden to examine all of the groups. Applicants' arguments have been considered but are not deemed persuasive. While the different inventions may be overlapping, they are not coextensive. As indicated in the Office Action mailed April 10, 2002, the proteins and DNA molecules of Inventions I, II, VIII, and IX differ structurally and functionally, as well as therapeutically. Furthermore, such differing molecules can be used in materially different methods which require different technical considerations and reagents, and in particular methods requiring different therapeutic considerations. The differences of Inventions I, II, VIII, and IX are underscored by their

divergent classification and independent search status. Thus, the examiner maintains that there would be undue burden of search to examine all the separate inventions. Furthermore, the products of Inventions VIII and IX are unrelated to the methods of Inventions III-VII because the DNA molecules cannot be made in or used by the methods of Inventions III-V. And, while Inventions I and II are related as product and process of use to Inventions III-VII, they are distinct because the proteins can be used to make antibodies which is a materially different method than that of Inventions III-VII (see MPEP § 806.05(h)).

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the examiner has shown a serious burden of search (see MPEP § 803). Therefore, the initial requirement of restriction for examination purposes as indicated is proper and therefore made FINAL.

Therefore, Claims 7-8, 17-47, and 55-63 are withdrawn as being drawn to non-elected subject matter and Claims 1-6, 11-16, 48-54, and 64-65 will examined on the merits in this Office Action.

Drawings

The drawings have been objected to by the draftsperson for the reasons cited on the attached Form PTO 948. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 15, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 15, and 53 are indefinite as to the metes and bounds of "protein's activity is salt tolerant". The Specification does not provide a definition for when a protein is considered salt tolerant but only implies that salt tolerant indicates a protein that maintains activity or structure at "high" salt concentrations. What is considered a "high" salt concentration or a "salt tolerant" protein would vary from individual to individual and would vary depending on the standard to which the protein was compared. Therefore, the metes and bounds of "salt tolerant" are not clear.

Claim 50 recites the limitation "the isolated heme-binding protein according to claim 47" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 48 and 49 from which it depends are drawn to a chimeric protein and do not mention an isolated heme-binding protein. Furthermore, even if Claim 50 was amended to recite "the chimeric protein of claim 49", it would not further limit the claim because the limitations that the protein comprises a heme binding domain and a signaling domain are already present in Claim 48 from which it depends.

Claim 65 recites the limitation "[t]he fragment according to claim 4" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 4 does not refer to a fragment.

Claims 1-5, 64, and 65 are indefinite because its unclear what myoglobin sequence is the reference sequence to which the claimed heme binding protein is compared. The claims require that the heme binding domains of the claimed proteins be at least 20% identical to a myoglobin heme binding domain. However, the sequences of myoglobin heme binding domains are diverse as evidenced by the sequence alignment shown below. Therefore, a protein may have a heme binding domain that is 20% identical to one particular myoglobin heme binding domain but not to another. Thus, the metes and bounds of the claims are unclear.

Comparison of Indian Elephant myoglobin (Acc. No. gi:70559) with that of myoglobin from Carp (Acc. No. gi:127647):

>gi|127647|sp|P02204|MYG_CYPCA Myoglobin
Length = 146

Score = 105 bits (262), Expect = 3e-23
Identities = 61/146 **(41%)**, Positives = 85/146 (58%), Gaps = 3/146 (2%)

Query: 8 ELVLKTWGKVEADIPGHGEFVLVRLFTGHPETLEKFDKFKHLKTEGEMKASEDLKKQGVT 67
ELVLK WG VEAD G G VL RLF HPET + F KF + + E+ + +K G T
Sbjct: 4 ELVLKCWGGVEADFEGTGGEVLTRLFKQHPETQKLFPKFVGIASN-ELAGNAAVKAHGAT 62

Query: 68 VLTALGGILKKKGHHEAEIQPLAQSHATKHKIPIKYLEFISDAIIHVLQSKHPAEFGADA 127
VL LG +LK +G H A ++PLA +HA HKI + I++ ++ V+ K A A
Sbjct: 63 VLKKLGELLKARGDHAAILKPLATTHANTHKIALNNFRLITEVLVKVMAEK--AGLDAGG 120

Query: 128 QGAMKKALELFRNDIAAKYKELGFQG 153
Q A+++ +++ DI YKE+GF G
Sbjct: 121 QSALRRVMDVVIGDIDTYYKEIGFAG 146

In addition, the claim is also unclear as to how many amino acids are considered part of the myoglobin heme-binding domain. Since the overall length of the sequence (in this case the heme binding domain) is taken in consideration when determining the percent identity between two proteins, the metes and bounds of when a protein is "at least 20% identical to a myoglobin heme binding domain" is unclear.

Claims 1-5, 11-15, 64 and 65 are indefinite as to the metes and bounds of "low affinity". Low is a relative term and the Specification does not define a specific quantitative value in order to ascertain when the affinity is low enough to meet the limitations of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (Proc. Natl. Acad. Sci (1996) Vol. 93, pp. 4649-4654 ; ref. 16 in IDS of Paper No. 4).

Zhang et al. teach a heme binding protein, HtB, which has 100% identity to the ~~sequence of SEQ ID NO:2 (see sequence alignment attached to this Office Action).~~ Zhang et al. teach that the proteins disclosed therein are from *Halobacterium salinarum*, a member of *Archaea* (p. 4649, Col. 1, last paragraph). The properties of a protein are a function of its sequence. Therefore, it is inherent that the HtB protein disclosed in

Zhang et al. has all of the properties of Claims 1-6 (such as reversibly binding oxygen with low affinity, having 20% identity to a myoglobin heme binding domain, salt tolerance, etc.) since these are the properties of the protein of SEQ ID NO: 2. Figure 5 (p. 4653) shows the SDS/PAGE analysis of the proteins from H. salinarum after fractionation of soluble and membrane-bound proteins (see Col. 1, lines 15-23). Thus, the protein disclosed in Zhang et al. is considered to be isolated by the fractionation and gel analysis.

Claims 1, 3-5, 11, 13-15, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Grinstaff et al. (U.S. Patent No. 5,635,207).

Grinstaff et al. teach and claim a method of preparing a blood substitute comprising myoglobin (see Claim 3). Myoglobin is considered a heme binding protein that reversibly binds oxygen with a low affinity and would have 100% identity to a myoglobin heme binding domain. The limitation in the present claims that the heme binding proteins are bacterial or that they are isolated from Archaea or H. salinarum has been treated similarly to a product-by-process (for example, protein made by the process of isolation from bacteria). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production" (see *In re Thorpe,* 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 MPEP 2113 and MPEP 2113)). In the instant case, the Specification does not provide a description of what features of the sequence identify a heme binding protein as being "bacterial" or from

Archaea or from H. salinarum. Thus, without such a description, the protein and blood substitute described in Grinstaff et al. appears to be patentably indistinguishable from that of the instant claims. It is an inherent property of myoglobin that its activity is "tolerant" to at least a small amount of salt (see rejections below for evidence of myoglobin's salt tolerance).

Claims 1, 3-5, 11, 13-15, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugimoto et al. (Biophysical Journal (Nov. 1998) 75: 2188-2194).

Sugimoto et al. disclose the expression, isolation, and purification of recombinant myoglobin from E. coli. Myoglobin is considered a heme binding protein that reversibly binds oxygen with low affinity and would have 100% identity to a myoglobin heme binding domain. The limitation in the present claims that the heme binding proteins are bacterial or that they are isolated from Archaea or H. salinarum has been treated similarly to a product-by-process (for example, protein made by the process of isolation from bacteria). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production" (see *In re Thorpe,* 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 MPEP 2113 and MPEP 2113)). In the instant case, the Specification does not provide a description of what features of the sequence identify a heme binding protein as being "bacterial" or from Archaea or from H. salinarum. Thus, without such a description, the protein and blood substitute described in Grinstaff et al. appears to be patentably indistinguishable from

that of the instant claims. The protein is contained in a 0.1 M potassium phosphate buffer and therefore appears to be "salt tolerant". Since the blood substitute compositions are not limited to having any components other than the heme binding protein, the composition of the purified myoglobin in buffer appears to meet the limitations of Claims 11-15. Thus, the reference meets the limitations of the claims.

Claims 1, 3-5, 11, 13-15, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (J. Biol. Chem. (Sept. 1995) 270(35): 20763-20774).

Zhao et al. disclose the expression, isolation, and purification of recombinant mutant myoglobin in E. coli (p. 20764, Col. 2, Materials and Methods). The L29F/H64Z mutant myoglobin is shown to bind oxygen with low affinity as compared to wild-type (see Table I). Therefore, the L29F/H64Z double mutant is considered a heme binding protein that reversibly binds oxygen with low affinity and would have greater than 20% identity to a myoglobin heme binding domain. The limitation in the present claims that the heme binding proteins are bacterial or that they are isolated from Archaea or H. salinarum has been treated similarly to a product-by-process (for example, protein made by the process of isolation from bacteria). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production" (see *In re Thorpe,* 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 MPEP 2113 and MPEP 2113)). In the instant case, the Specification does not provide a description of what features of the sequence identify a heme binding protein as being

"bacterial" or from Archaea or from H. salinarum. Thus, without such a description, the protein and blood substitute described in Grinstaff et al. appears to be patentably indistinguishable from that of the instant claims. The protein is contained in a 0.1 M potassium phosphate buffer and therefore appears to be "salt tolerant". Zhao et al. teach that the disclosed double mutant was constructed for use as a blood substitute (see abstract). Thus, the reference meets the limitations of the claims.

Claims 1-5, 11-15, and 64-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Gong et al. (Proc. Natl. Acad. Sci. (Dec. 1998) 95: 15177-15182).

Gong et al. teach the expression and purification of FixL from B. japonicum. The FixL protein contains a heme binding domain and appears to bind oxygen reversibly and with low affinity (see Table 2 and compare binding constant with wild-type and mutant myoglobins). Since the claims do not indicate how many amino acids are considered the "heme binding domain" nor what myoglobin sequence the claimed proteins are to be compared, the fixL protein is considered to have at least 20% identity to the appropriate myoglobin sequence and length given the appropriate sequence matching conditions. The FixL sequence contains a histidine kinase signaling domain (p. 15177, Col. 2, first paragraph). The limitation in the present claims that the heme binding proteins are bacterial or that they are isolated from Archaea or H. salinarum has been treated similarly to a product-by-process (for example, protein made by the process of isolation from bacteria). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product

itself. The patentability of a product does not depend on its method of production" (see *In re Thorpe,* 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 MPEP 2113 and MPEP 2113)). In the instant case, the Specification does not provide a description of what features of the sequence identify a heme binding protein as being "bacterial" or from Archaea or from H. salinarum. Thus, without such a description, the protein described in Gong et al. appears to be patentably indistinguishable from that of the instant claims. Moreover, the FixL protein is purified and placed in a buffer containing salt (p. 15177, Col. 2, "Overexpression and Protein Purification"). Therefore, the protein is considered "salt tolerant" and, absent evidence of a component in the claimed blood substitute that is not present in the composition of Gong et al., the Gong et al. composition containing the FixL protein is considered patentably indistinguishable from the blood substitute compositions of Claims 11-15. Thus, the claims are anticipated over the prior art.

Claim Objections

Claims 12-16, 49-54, and 64-65 are objected to for incorrect dependency due to the renumbering of the claims. Correction of the dependency in these claims is required.

Claim 16 is also objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

Claims 1-6, 11-15, 50, 53, and 64-65 are rejected. Claims 12-16, 49-54, and 64-65 are objected to, and Claim 48 appears to be in condition for allowance.

It appears that there is no teaching or suggestion in the prior art of a chimeric protein comprising a bacterial heme binding domain and a heterologous signaling domain or a blood substitute comprising the protein of SEQ ID NO:2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
February 4, 2003

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